application data sheet constitutes the specific reference required by 35 U.S.C. **119(e)** or **120**, and **§ 1.78(a)(2)** or **§ 1.78(a)(4)**, and need not otherwise be made part of the specification.

The Office Action states at paragraph 7 that the sequence listing indicates in field <212> that the molecule of SEQ ID NO:7 is a polypeptide. Applicants respectfully submit that the seqlist properly identifies the molecule:

<210> 7
<211> 1774
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (263)...(1547)

Withdrawal of the objections is requested.

Claims 1-10 have been rejected under 35 U.S.C. 112, first paragraph. Without conceding to the correctness of the rejection, Claim 1 has been amended to recite a molecule that encodes the polypeptide of SEQ ID NO:8. Claims 3 and 4 have been amended to recite a fragment of at least 100 nucleotides of SEQ ID NO:7. Claim 6 has been amended to recite specific exemplary stringent hybridization conditions. Applicants respectfully submit that the present claims meet the requirements of 35 U.S.C. 112, first paragraph.

The claims to fragments have been rejected by the Examiner as "broadening out" the scope of the claim. As stated in the written description guidelines, "there is no basis for a per se rule [for] . . . limiting DNA claims to only the sequence disclosed." There is no reason to exclude polynucleotide fragments from patent protection, or to demand that all claims to DNA be required to use "consisting of" language.

The fragments set forth in Claims 3 and 4 provide for a sequence as disclosed in the specification. These fragments find use, for example, in detecting the upregulation of Grail during induction of anergy. The role of immune function in many chronic and serious diseases makes the detection of anergy useful in the evaluation of the pathophysiology or immunotherapy of cancer, autoimmune disease, and transplant rejection. The fact that an unrelated sequence could be "tagged" onto the ends of a fragment would not change its purpose, or its ability to detect anergy.

The Office Action states that there is insufficient guidance as to the additional nucleotides and "whether the resulting polynucleotide after additional nucleotide would maintain both structure and function as the claimed polynucleotide . . . there is insufficient working example demonstrating

that adding additional nucleotide to the fragment of SEQ ID NO:7 would encode the same protein, much less maintain the structure and function of the protein."

Applicants respectfully submit that any number of sequences may be added to a polynucleotide fragment – such as vector sequences, targeting sequences, sequences for purification, and the like. Such sequences need not be coding sequences, and in fact can be regulatory elements, sequences providing for replication, or in fact mere "junk" DNA whose only purpose is to avoid patent infringement.

The DNA sequences of the present invention have many uses that are completely unrelated to producing a polypeptide, because the nucleotide sequence itself is a useful marker. In the evaluation of immune function and treatment, as described above and in the specification, it is useful to mark the induction of anergy, which can be detected by determining the presence of the GRAIL sequence.

It is quite predictable that additional sequences will not change the ability of a DNA fragment to hybridize to the complementary sequence. As is known in the art, hybridization kinetics are determined by the number of contiguous complementary nucleotides. The number of external unrelated nucleotides does not alter the hybridization patterns. Indeed, if such were the case, it would not be possible to perform hybridizations to genomic sequences – however such are routinely utilized throughout the world of molecular biology. One does not deny copyright protection to a song because it can be made into a record with other songs, and a DNA sequence should not be denied patent protection merely because it could be provided with alternative flanking sequences.

The Office Action states that Claim 6 "encompasses any random nucleotide of any length which hybridizes under undisclosed "stringent conditions" that may or may not bind specifically to SEQ ID NO:7". Applicants respectfully submit that this is not true. Claim 6 has been amended to recite specific exemplary stringent hybridization conditions, as set forth in the specification in paragraph 24.

As is well-known from innumerable studies of hybridization kinetics, the ability of two complementary sequences to hybridize under particular conditions can be exactly worked out by a formula based on the temperature of the reaction, the percentage of GC and AT pairs, the ionicity of the reaction, and the length of the sequence. The temperature and ionicity are set forth in the claims, and the percentage of AT and GC pairs are easily determined by looking at SEQ ID NO:7. The length of identity required for hybridization under stringent conditions is, on average, around 200 nucleotides. While increasing length does not change the dynamics (as discussed above), a shorter sequence will fail to bind under the stated conditions. The claim therefore by definition cannot encompass any random nucleotide of any length, because only sequences with a high

degree of similarity to the provided sequence, and having sufficient length to form a stable duplex are encompassed by the claims.

Further, by definition the claim requires specific binding, because hybridization under stringent conditions *is* specific binding.

In view of the above amendments and remarks, withdrawal of the rejection is requested.

Claims 1 and 7-10 have been rejected under 35 U.S.C. 102(b) as anticipated by U.S. Patent no. 5,747,299. Applicants have amended Claim 1 to recite molecules specifically related to the provided SEQ ID NO:7, which sequence has no homology to the sequences set forth in U.S. 5,747,299. Withdrawal of the rejection is requested.

Claims 3-6 have been rejected under 35 U.S.C. 102 as being anticipated by U.S. Patent no. 5,989,549, which teaches a fragment that is 77 nucleotides identical to SEQ ID NO:7. Applicants have amended the pending claims to recite a fragment of at least 100 nucleotides. The reference fails to teach a sequence meeting the limitations of the claims. Withdrawal of the rejection is requested.

CONCLUSION

Applicants submit that all of the claims are now in condition for allowance, which action is requested. If the Examiner finds that a Telephone Conference would expedite the prosecution of this application, she is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any other fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number STAN-177.

Respectfully submitted,

Date: February 5, 2003

By: _____
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APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

Substitute Paragraphs 26, 28, 50 and 51 with the following rewritten paragraphs:

[26] Nucleic acids encoding *GRAIL* may be cDNA or genomic DNA or a fragment thereof. The term "*GRAIL* gene" shall be intended to mean the open reading frame encoding specific *GRAIL* polypeptides, introns, as well as adjacent [5 or 3] 5' or 3' non-coding nucleotide sequences involved in the regulation of expression, up to about 20 kb beyond the coding region, but possibly further in either direction. The gene may be introduced into an appropriate vector for extrachromosomal maintenance or for integration into the host.

[28] A genomic sequence of interest comprises the nucleic acid present between the initiation codon and the stop codon, as defined in the listed sequences, including all of the introns that are normally present in a native chromosome. It may further include the [5 or 3] 5' or 3' untranslated regions found in the mature mRNA. It may further include specific transcriptional and translational regulatory sequences, such as promoters, enhancers, *etc.*, including about 1 kb, but possibly more, of flanking genomic DNA at either the [5 or 3] 5' or 3' end of the transcribed region. The genomic DNA may be isolated as a fragment of 100 kbp or smaller; and substantially free of flanking chromosomal sequence. The genomic DNA flanking the coding region, either 3' or 5', or internal regulatory sequences as sometimes found in introns, contains sequences required for proper tissue and stage specific expression.

[50] A number of methods are available for analyzing nucleic acids for the presence or quantity of a specific sequence, *e.g.* a disease associated polymorphism, changes in expression profile between a responsive and anergic cell, *etc.* Cells that are suspected of an anergic state may be used as a source of mRNA, which may be assayed directly or reverse transcribed into cDNA for analysis. The nucleic acid may be amplified by conventional techniques, such as the polymerase chain reaction (PCR), to provide sufficient amounts for analysis. The use of the polymerase chain reaction is described in Saiki, *et al.* (1985) Science 239:487, and a review of techniques may be found in Sambrook, *et al.* Molecular Cloning: A Laboratory Manual, CSH Press 1989, [pp.14.2 14.33] pp.14.2-14.33. Alternatively, various methods are known in the art that utilize oligonucleotide ligation as a means of detecting polymorphisms, for examples see Riley *et al.* (1990) N.A.R. 18:2887-2890; and Delahunty *et al.* (1996) Am. J. Hum. Genet. 58:1239-1246.

[51] A detectable label may be included in an amplification reaction. Suitable labels include fluorochromes, *e.g.* fluorescein isothiocyanate (FITC), rhodamine, Texas Red, phycoerythrin, allophycocyanin, 6-carboxyfluorescein (6-FAM), [2 ,7 -dimethoxy-4 ,5 -dichloro-6-carboxyfluorescein (JOE), 6-carboxy-X-rhodamine (ROX), 6-carboxy-2 ,4 ,7 ,4,7-hexachlorofluorescein (HEX), 5-carboxyfluorescein (5-FAM) or N,N,N ,N -tetramethyl-6-carboxyrhodamine (TAMRA)] 2′,7′-dimethoxy-4′,5′-dichloro-6-carboxyfluorescein (JOE), 6-carboxy-X-rhodamine (ROX), 6-carboxy-2′,4′,7′,4,7-hexachlorofluorescein (HEX), 5-carboxyfluorescein (5-FAM) or N,N,N′,N′-tetramethyl-6-carboxyrhodamine (TAMRA), radioactive labels, *e.g.* ^{32}P, ^{35}S, ^{3}H; *etc.* The label may be a two stage system, where the amplified DNA is conjugated to biotin, haptens, *etc.* having a high affinity binding partner, *e.g.* avidin, specific antibodies, *etc.*, where the binding partner is conjugated to a detectable label. The label may be conjugated to one or both of the primers. Alternatively, the pool of nucleotides used in the amplification is labeled, so as to incorporate the label into the amplification product.

Cancel claims 2 and 11-19.

1. (amended) An isolated nucleic acid molecule other than a naturally occurring chromosome comprising a sequence encoding [a GRAIL protein] the amino acid sequence set forth in SEQ ID NO:8.

3. (amended) An isolated nucleic acid molecule according to Claim [2] 1, wherein said nucleic acid comprises the nucleotide sequence set forth in [SEQ ID NO:5 or] SEQ ID NO:7[; or a fragment thereof].

4. (amended) An isolated nucleic acid comprising at least [18] 100 contiguous nucleotides of the sequence of [SEQ ID NO:5 or] SEQ ID NO:7.

5. (amended) An isolated nucleic acid [comprising] consisting of at least [50] 100 contiguous nucleotides of the sequence of [SEQ ID NO:5 or] SEQ ID NO:7.

6. (amended) An isolated nucleic acid that hybridizes under stringent conditions at 50°C or higher and 0.1XSSC (15 mM NaCl/01.5 mM Na citrate) to the nucleic acid sequence of [SEQ ID NO:5 or] SEQ ID NO:7.